

p-HYDROXY-*m*-METHOXYPHENYLETHYLAMINE
AND THE RESOLUTION OF
a-p-HYDROXYPHENYLETHYLAMINE

BY

CHARLES W. MOORE, PH.D.

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES
FREDERICK B. POWER, PH.D., LL.D., *Director*
6, King Street, Snow Hill
LONDON, E.C.

LII.— *α -p-Hydroxy-m-methoxyphenylethylamine and the Resolution of α -p-Hydroxyphenylethylamine.*

By CHARLES WATSON MOORE.

It has several times recently been shown that the enantiomorphously related compounds may differ considerably in their physiological action. Thus, Cushny (*J. Physiol.*, 1904, **30**, 176) has shown that *l*-hyoscyamine is considerably more active physiologically than the corresponding *d*-base (compare also *Trans.*, 1909, **95**, 1969). Similarly, the same author has noted (*Pharm. Journ.*, 1909, **82**, 56) that the stereoisomeric epinephrines ("adrenalines") (β -3:4-trihydroxy- β -phenylethylmethyamines) show great differences in the relative intensities of their effect on the blood pressure.

The base α -*p*-hydroxyphenylethylamine, described by Tutin, Caton, and Hann (*Trans.*, 1909, **95**, 2113), exerts an action on the

blood pressure somewhat similar to that of epinephrine, although in a less degree, and, since the former base contains an asymmetric carbon atom, it was considered of interest to ascertain whether the optically active bases, obtained by its resolution, would differ in physiological activity. α -*p*-Hydroxyphenylethylamine *d*-camphor-sulphonate was therefore prepared and submitted to fractional crystallisation, when the salt of the levorotatory base was easily obtained in a pure condition.

l- α -*p*-Hydroxyphenylethylamine *d*-camphorsulphonate melts at 203—205°, and the specific rotation of the base contained in it, calculated from that of the salt, is $[\alpha]_D - 7.9^\circ$. The salt of the *d*-base could not be obtained in a pure condition, the specific rotation of the base contained in it being $[\alpha]_D + 6.9^\circ$. Optically pure benzoyl derivatives were, however, obtained from both of the stereoisomeric bases. The effect on the blood pressure of the *l*- and *dl*-bases was determined by Dr. H. H. Dale, of the Wellcome Physiological Research Laboratories, to whom the author now expresses his thanks. No difference in physiological activity between the two bases was observed, and it is therefore evident that in this case the enantiomorphous forms possess an equal degree of physiological activity.

A quantity of acetovanillone (4-hydroxy-3-methoxyacetophenone) being available, it was considered of interest to prepare the corresponding α -*p*-hydroxy-m-methoxyphenylethylamine from it. This compound was obtained by the reduction of acetovanilloneoxime, and its hydrochloride and benzoyl derivatives have also been characterised. It has been found by Dr. H. H. Dale, as was anticipated, that the hydroxymethoxy-base is slightly less active physiologically than the above-mentioned α -*p*-hydroxyphenylethylamine.

EXPERIMENTAL.

α -p-Hydroxy-m-methoxyphenylethylamine.

Acetovanillone (4-hydroxy-3-methoxyacetophenone), as obtained from the rhizome of *Apocynum androsaemifolium*, Linné (Moore, Trans., 1909, **95**, 734), was converted into its oxime in the usual manner.

Eighteen grams of acetovanilloneoxime were dissolved in 250 c.c. of aqueous methyl alcohol, and twice the theoretical amount of 3 per cent. sodium amalgam gradually introduced, the mixture being kept acid by the frequent addition of acetic acid. When all reaction had ceased, water was added, the alcohol distilled off, and the aqueous liquid extracted with ether to remove unchanged oxime, after which it was rendered alkaline by means of sodium carbonate, and thoroughly extracted with amyl alcohol. The amyl-

alcoholic liquids were extracted with successive quantities of dilute hydrochloric acid, and the combined acid liquids concentrated under diminished pressure, when, on cooling, *α -p-hydroxy-m-methoxyphenylethylamine hydrochloride* separated in glistening prisms. This salt is readily soluble in water and alcohol, but can be recrystallised from a mixture of alcohol and ethyl acetate. The quantity so obtained amounted to about 8.5 grams:

0.1490 gave 0.2938 CO_2 and 0.0936 H_2O . $\text{C}=53.7$; $\text{H}=7.0$.

0.1710 „ 0.1180 AgCl . $\text{Cl}=17.0$.

$\text{C}_9\text{H}_{13}\text{O}_2\text{N}\cdot\text{HCl}$ requires $\text{C}=53.1$; $\text{H}=6.9$; $\text{Cl}=17.4$ per cent.

A methoxyl determination by Perkin's modification of the Zeisel method gave the following result:

0.2136 gave 0.2445 AgI . $\text{OMe}=15.1$.

$\text{C}_8\text{H}_{11}\text{ONCl}\cdot\text{OMe}$ requires $\text{OMe}=15.2$ per cent.

α -p-Hydroxy-m-methoxyphenylethylamine was obtained from its hydrochloride by the action of sodium ethoxide on an alcoholic solution of the salt. Five grams of the hydrochloride were dissolved in about 25 c.c. of warm absolute alcohol, and to the solution 0.53 gram of sodium, dissolved in 10 c.c. of absolute alcohol, was added. The precipitated sodium chloride was removed by filtration, and the filtrate cooled, when the *base* separated in glistening prisms, melting at 158° . The quantity so obtained was only 1.5 grams, and on concentrating the alcoholic mother liquor, only amorphous products were obtained. As only 95 per cent. of the theoretical amount of sodium ethoxide was employed for the liberation of the base, this change can only be attributed to the unstable nature of the substance in solution. A similar phenomenon was observed on recrystallising the base, but the latter, when in the crystalline state, is quite stable:

0.1338 gave 0.3180 CO_2 and 0.0970 H_2O . $\text{C}=64.8$; $\text{H}=8.0$.

0.2806 „ 20.6 c.c. N_2 at 23° and 755 mm. $\text{N}=8.2$.

$\text{C}_9\text{H}_{13}\text{O}_2\text{N}$ requires $\text{C}=64.7$; $\text{H}=7.8$; $\text{N}=8.4$ per cent.

A methoxyl determination by Perkin's modification of the Zeisel method gave the following result:

0.2240 gave 0.3095 AgI . $\text{OMe}=18.2$.

$\text{C}_8\text{H}_{10}\text{ON}\cdot\text{OMe}$ requires $\text{OMe}=18.5$ per cent.

The *dibenzoyl* derivative, prepared by the Schotten-Baumann method, crystallises from alcohol in glistening plates, melting at 178° :

0.1326 gave 0.3574 CO_2 and 0.0686 H_2O . $\text{C}=73.5$; $\text{H}=5.7$.

$\text{C}_{23}\text{H}_{21}\text{O}_4\text{N}$ requires $\text{C}=73.6$; $\text{H}=5.6$ per cent.

α -p-Hydroxy-m-methoxy-N-benzoylphenylethylamine was obtained by heating the dibenzoyl derivative for some hours with a 10 per

cent. alcoholic solution of potassium hydroxide. It crystallises from alcohol in glistening needles, melting at 168° :

0.1230 gave 0.3170 CO_2 and 0.0711 H_2O . $\text{C}=70.3$; $\text{H}=6.4$.

$\text{C}_{16}\text{H}_{17}\text{O}_3\text{N}$ requires $\text{C}=70.1$; $\text{H}=6.3$ per cent.

The Resolution of α -p-Hydroxyphenylethylamine.

α -p-Hydroxyphenylethylamine hydrochloride was first prepared by Tutin, Caton, and Hann (*loc. cit.*), by the reduction of *p*-hydroxyacetophenoneoxime, according to the above-described method for the preparation of α -p-hydroxy-*m*-methoxyphenylethylamine hydrochloride. The yield of hydrochloride obtained by these authors was only about 30 per cent. of the theoretical. In view of the above-recorded observation respecting the instability of α -p-hydroxy-*m*-methoxyphenylethylamine, it seemed advisable to isolate α -p-hydroxyphenylethylamine hydrochloride without ever liberating the free base. The following modification of the original method was accordingly employed.

Twenty-seven grams of *p*-hydroxyacetophenoneoxime were dissolved in 300 c.c. of aqueous methyl alcohol, and twice the theoretical amount of 3 per cent. sodium amalgam gradually introduced, the mixture being kept acid by the frequent addition of acetic acid. When the reduction was finished, hydrochloric acid, in slight excess, was added, and the solution evaporated to complete dryness under diminished pressure. During the concentration most of the sodium chloride separated, and was removed by filtration. The final residue consisted of the hydrochloride of the base, together with a little sodium chloride, from which the former was obtained by extraction with cold absolute alcohol. The yield was about 70 per cent. of the theoretical.

α -p-Hydroxyphenylethylamine *d*-camphorsulphonate was obtained by the interaction of α -p-hydroxyphenylethylamine hydrochloride and silver *d*-camphorsulphonate in aqueous solution. The precipitated silver chloride was removed by filtration, and the filtrate evaporated to dryness under diminished pressure.

1- α -p-Hydroxyphenylethylamine *d*-Camphorsulphonate.—The crystalline camphorsulphonate thus obtained was dissolved in hot absolute alcohol, when, on keeping for a short time, a crop of crystals was obtained, melting at 200 — 202° . On recrystallisation from alcohol, the melting point rose to 203 — 205° , when it remained constant. The salt forms small, glistening plates, readily soluble in water and hot alcohol:

0.3154 gave 0.2010 BaSO_4 . $\text{S}=8.7$.

$\text{C}_{18}\text{H}_{27}\text{O}_5\text{NS}$ requires $\text{S}=8.7$ per cent.

0.4838, made up to 20 c.c. with water, gave, in a 2-dcm. tube, $\alpha_D + 0^\circ 32'$, whence $[\alpha]_D + 11.0^\circ$; $[M]_D + 40.6^\circ$.

0.4480, made up to 20 c.c. with water, gave, in a 2-dcm. tube, $\alpha_D + 0^\circ 29'$, whence $[\alpha]_D + 10.8^\circ$; $[M]_D + 39.8^\circ$.

The molecular rotation of *d*-camphorsulphonic acid is $[M]_D + 51^\circ$, whence the basic ion has $[\alpha]_D - 7.9^\circ$.

The 1-*dibenzoyl* derivative, prepared by the Schotten-Baumann method, crystallises from alcohol in long needles, melting at 210° :

0.1452 gave 0.4090 CO_2 and 0.0745 H_2O . $\text{C} = 76.8$; $\text{H} = 5.7$.

$\text{C}_{22}\text{H}_{19}\text{O}_3\text{N}$ requires $\text{C} = 76.5$; $\text{H} = 5.5$ per cent.

A determination of its specific rotatory power gave the following result:

0.3502, made up to 20 c.c. with chloroform, gave $\alpha_D - 0^\circ 40'$ in a 2-dcm. tube, whence $[\alpha]_D - 19.0^\circ$.

1- α -p-Hydroxy-N-benzoylphenylethylamine was formed on heating the dibenzoyl derivative with a 10 per cent. alcoholic solution of potassium hydroxide. It crystallised from dilute methyl alcohol in small, glistening needles, containing 1.5 molecules of water of crystallisation. The anhydrous substance melts at 144° . This substance appears to be dimorphous, as the racemic modification, prepared by Tutin, Caton, and Hann (*loc. cit.*), forms large, hexagonal prisms, melting at 156° :

0.5040 (air dried) gave, on heating at 110° , 0.0495 H_2O . $\text{H}_2\text{O} = 9.8$.

0.1388 * gave 0.3804 CO_2 and 0.0794 H_2O . $\text{C} = 74.7$; $\text{H} = 6.3$.

$\text{C}_{15}\text{H}_{15}\text{O}_2\text{N} \cdot 1.5\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 10.0$ per cent.

$\text{C}_{15}\text{H}_{15}\text{O}_2\text{N}$ requires $\text{C} = 74.8$; $\text{H} = 6.2$ per cent.

A determination of its specific rotatory power gave the following result:

0.2150,* made up to 20 c.c. with chloroform, gave $\alpha_D - 1^\circ 8'$ in a 2-dcm. tube, whence $[\alpha]_D - 52.7^\circ$.

The alcoholic mother liquor from which the first crop of crystals had been removed, as above described, was concentrated to a small volume, when a quantity of crystals, melting from 180° to 190° , was obtained. This was removed, and the mother liquor mixed with a large volume of ethyl acetate, when it yielded a final fraction, melting at 163 — 165° . This final fraction consisted largely of the salt of the dextrorotatory modification, but all attempts to obtain it pure were unsuccessful.

A determination of its specific rotatory power gave the following result:

* Anhydrous substance.

0.4338, made up to 20 c.c. with water, gave $\alpha_D + 0^\circ 42.7'$ in a 2-dcm. tube, whence $[\alpha]_D + 16.4^\circ$; $[M]_D + 60.5^\circ$.

The molecular rotation of *d*-camphorsulphonic acid is $[M]_D + 51^\circ$, whence the basic ion has $[\alpha]_D + 6.9^\circ$.

The *d*-dibenzoyl derivative, prepared by the Schotten-Baumann method, crystallised from alcohol in long needles, melting at 205° . After recrystallising from ethyl acetate, the melting point was constant at 210° :

0.1460 gave 0.4104 CO_2 and 0.0745 H_2O . $\text{C} = 76.6$; $\text{H} = 5.6$.

$\text{C}_{22}\text{H}_{19}\text{O}_3\text{N}$ requires $\text{C} = 76.5$; $\text{H} = 5.5$ per cent.

A determination of its specific rotatory power gave the following result:

0.3348, made up to 20 c.c. with chloroform, gave $\alpha_D + 0^\circ 37'$ in a 2-dcm. tube, whence $[\alpha]_D + 18.4^\circ$.

d- α -p-Hydroxy-N-benzoylphenylethylamine was formed on heating the dibenzoyl derivative with a 10 per cent. solution of alcoholic potassium hydroxide. It crystallises from dilute methyl alcohol in glistening needles, containing 1.5 molecules of water of crystallisation. The anhydrous substance melts at 144° :

0.2850 (air dried), on heating at 110° , lost 0.0275 H_2O . $\text{H}_2\text{O} = 9.6$.

0.1410 * gave 0.3880 CO_2 and 0.0796 H_2O . $\text{C} = 75.0$; $\text{H} = 6.2$.

$\text{C}_{15}\text{H}_{15}\text{O}_2\text{N}, 1.5\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 10.0$ per cent.

$\text{C}_{15}\text{H}_{15}\text{O}_2\text{N}$ requires $\text{C} = 74.8$; $\text{H} = 6.2$ per cent.

A determination of its specific rotatory power gave the following result:

0.1494,* made up to 20 c.c. with chloroform, gave $\alpha_D + 0^\circ 49'$ in a 2-dcm. tube, whence $[\alpha]_D + 54.6^\circ$.

In conclusion, the author wishes to express his thanks to Mr. Frank Tutin for suggesting this investigation.

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LONDON, E.C.

* Anhydrous substance.

